

Bristol-Myers Squibb Pharmaceutical Research Institute

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June 2, 2005

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Dockets Management Branch
Food and Drug Administration, HFA-305
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 2005D-0112; Draft Guidance for Industry on Clinical Trial Endpoints for the Approval of Cancer Drugs & Biologics (Federal Register, volume 70, number 63, page 17095, 04 Apr 2005)

Dear Sir or Madam:

Bristol-Myers Squibb (BMS), a diversified worldwide health and personal care company with principal businesses in pharmaceuticals, infant formulas, and nutritional products, is pleased to have the opportunity to offer comments on the "*Draft Guidance for Industry on Clinical Trial Endpoints for the Approval of Cancer Drugs & Biologics*." Our company's mission is to extend and enhance human life by providing the highest-quality pharmaceutical and related health care products. As an important part of this mission includes efforts to discover, develop, and deliver new oncology therapies to patients, we provide comments on this important new draft guidance.

We commend the FDA for development of a constructive draft guidance that addresses many of the critical problems in designing and analyzing registration studies in oncology. This introduction of standard terminology and approach should be of benefit to industry and FDA reviewers. We particularly look forward to subsequent guidances (as mentioned in lines 29-30 of this draft guidance) that will focus on specific cancer types (e.g., lung cancer, colon cancer). There are several aspects of the current draft guidance that could be modified to provide even more clarity regarding clinical registration studies in oncology.

Summary of BMS Comments on Draft Guidance

While detailed comments are outlined below, we provide comments in the following general areas:

- We propose modifications to wording describing the role and use of independent assessments and sensitivity analyses in time-based tumor assessment measures
- We recommend consistent use of standard terminology when referring to comparisons (or historical contrast) to approved or available agents for determination of accelerated approval
- Based upon historical data, we propose increased emphasis on the utility of single arm trials in accelerated approval, especially for solid tumors
- We highlight complications and concerns regarding the topics of non-inferiority and isolating drug effect for combination products and ask FDA to consider a workshop or ODAC deliberation on these topics culminating in development of subsequent oncology-specific guidances.

2005D-0112



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Specific Comments (with Clarifications Requested and Recommended Actions)

III. General Endpoint Considerations

B. Endpoints based on Tumor Assessments

Lines 200-210: We propose further clarification on the broad statements regarding need for independent central review. While there is value for this type of analysis in unblinded trials of small to moderate size, a full blinded independent analysis presents practical complications in large trials, and limited added value may be obtained from the extensive independent analysis effort for a randomized blinded study. Further, in the case of large trials evaluating DFS, the use of multiple sensitivity analyses historically served well to confirm the robustness of results.

Recommendation: We propose that FDA add clarification (new sentence in line 204 between existing sentences) that “*Centralized independent verification of tumor endpoint assessments (especially for PFS or DFS) may not be necessary when randomized trials are blinded (unless side effect profile would substantially “unblind” the trial in practice) or effect sizes are robust in large randomized trials where sensitivity analysis supports lack of observer bias (especially for DFS).*”

Lines 239-241: A revision is suggested that would delete “likely” in this sentence. An addition of timing is suggested.

Recommendation: “*Unscheduled assessments can occur... differences between study arms in the frequency, timing, or reason for unscheduled assessment may introduce bias.*”

Line 279-282: The draft guidance states that “These issues, in addition to an assessment of benefits of existing therapies, determine whether ORR will support marketing authorization, either for regular approval...or for accelerated approval...” The use of the term “existing” therapies in this context is unclear. Further, in several places in the draft guidance different terminology of unclear meaning is used to describe background therapies of interest relative to accelerated approval. Given the clear regulatory definition of the terms approved therapy or available therapy (should an approved therapy not exist; we note the July 2004 FDA guidance on available therapy and reference to available therapy in several other sections of this draft guidance – eg, lines 125-126 and 190-191), we suggest using these terms to bring greater clarity when discussing accelerated approval and the needs for comparison or contrast of performance vs some alternate therapy.

Recommendation: We recommend to change line 280: “of existing therapies, determine whether ORR will support marketing authorization” to “*approved or available therapies.*” Similarly in line 544-545 we recommend changing “effective therapy” to “*approved or available therapies*”

Lines 291-293: The draft guidance states that time to symptomatic progression, which would represent a clear clinical benefit, is infrequently assessed but would be a credible endpoint of a well-conducted (generally blinded) trial.

Recommendation: Although this will vary by tumor type, we suggest inclusion of examples where time to symptomatic progression would be an appropriate endpoint. Further, please provide a definition of “time to symptomatic progression” and consider inclusion as an option in Table 1, with the advantages and disadvantages. If this is the same as “time to progression of cancer symptoms” at Line 462, then a reference to this section would be helpful.

Line 361-376: The types of sensitivity analyses mentioned in this paragraph that are to be prespecified in the study analysis plan are dependent on the pattern of missing data observed. We propose that the guidance should mention that the analysis plan may specify that certain types of sensitivity analyses may be done only if certain criteria and missing data patterns are observed (eg, number of unscheduled visits, use of secondary therapy).

Recommendation: We recommend to add the following sentence to end of line 368: *“It is reasonable that the analysis plan may include specific sensitivity analyses to be conducted under certain observed data conditions.”* We also recommend to add the following to the end of line 376: *“If an imbalance is noted in the use of secondary therapy between treatment arms, the proposed sensitivity analysis could more appropriately allow for censoring of subjects at the time of initiation of secondary therapy for maintenance of therapeutic effect.”*

Line 361-394: The draft guidance proposes numerous sensitivity analyses, but does not address issues of multiplicity, especially for type II error. All of the proposed sensitivity analyses reduce the number of events and potentially decrease the power of the treatment comparison. It would not be clear whether lack of statistical significance observed in sensitivity analyses would be due to removal of bias or power loss.

Recommendation: We recommend that FDA acknowledge the aspect of power loss by stating that the primary objective of sensitivity analyses is to evaluate for bias rather than retest for statistical significance of the original finding.

Lines 367-368: The draft guidance states it is important to pre-specify one or more sensitivity analyses for PFS. Pre-specification of analysis is normally considered for type I error protection. The most relevant sensitivity analyses would be defined after observing the pattern of missing data.

Recommendation: We recommend to add a table showing the correspondence between patterns of missing data and appropriate sensitivity analyses.

III. General Endpoint Considerations

C. Endpoints Involving Symptom Assessment

Lines 503-504: The draft guidance states that: “Ideally, when patients stop treatment, data collection forms should continue to gather information to inform the analysis.”

Recommendation: We recommend to define how long patients should be followed (eg, for 30 days after the last dose).

IV. Endpoints and Clinical Trial Design; Selected Issues

A. Single Arm Trials

Lines: 542-558: A review of historical data supports that single-arm studies are useful in providing earlier access to useful new therapies under accelerated approval provisions of 21CFR 314, SubPart H (supported by earlier review of Dagher et al; JNCI 2004). In cases where full randomized trials were subsequently completed with these agents, these trials often show definitive clinical benefit justifying full approval. Perhaps the situation for rare hematologic malignancies might require a reanalysis. Of the 21 drugs that received accelerated (Subpart H) approval, as of May 2005, the vast majority did so through single-agent, single-arm trials. Of those 21 agents, 7 received full approval confirmation through subsequent randomized trials (Camptosar, Eloxatin, Gleeevec, Taxotere, Temodar, Xeloda and Zinecard), 3 received full approvals for related indications (Arimidex, Ethyol, Femara), and 2 had published randomized trials demonstrating clinical benefit (Doxil and Erbitux). Of the remaining 9 agents, 7 pertain to hematologic malignancies (Bexxar, Campath, Clolar, DepoCyt, Mylotarg, Ontak and Zevalin), and the last 2 (Celebrex and Iressa) actually received their initial accelerated approval based upon randomized trials, not confirmed by definitive trials in the latter case.

Recommendation: While not perfect, given the benefit to patients of an effective accelerated approval approach for oncology drugs, we suggest stronger emphasis be provided to clarifying the overall effective functioning of the accelerated approval system when the mandated Phase III trials were conducted to confirm definitive clinical benefit. This is particularly valid for solid tumors.

Lines 544-545: As noted for lines 279-282, the use of the term “effective” therapy in this context may be unclear (“In settings where there is no effective therapy and where...”. Further, in several places in the draft guidance different terminology of unclear meaning is used to describe background therapies of interest relative to accelerated approval (existing therapy, effective therapy, and available therapy are all used). Given the clear regulatory definition of the terms approved therapy or available therapy (should an approved therapy not exist; we note the July 2004 FDA guidance on available therapy and reference to available therapy in several other sections of this draft guidance – eg, lines 125-126 and 190-191), we support the use of these terms to bring greater clarity when discussing accelerated approval and the needs for comparison or contrast of performance vs some alternate therapy.

Recommendation: We recommend to change “ effective therapy” to “*approved or available therapy*”

IV. Endpoints and Clinical Trial Design; Selected Issues

B. Noninferiority

Lines 561-602: The recent FDA position on non-inferiority trials has raised concerns among sponsors, investigators and patients. Whereas, in general, superiority (in efficacy) designs highlight therapeutic progress, it is also true that novel approaches to molecular selection of the appropriate patient population will not be limited only to efficacy markers but also to safety markers. In this

context, the development of individualized treatment that could improve tolerance but not necessarily affect activity might be penalized by an excessively rigid approach to non-inferiority, and particularly so as the size of populations to be studied will be smaller, and not larger, than the historical norm. BMS acknowledges the challenges identified by FDA regarding non-inferiority study designs. In particular, designs in which the non-inferiority margin is set to retain a fraction of the control drug's effect (eg, 50%) can be prohibitively large, as acknowledged by FDA. This is not realistic for prospectively conducted trials in the era of targeted, individualized therapy. Alternative ideas are needed. Large studies mainly arise when the control regimen is chosen as the standard of care that has itself demonstrated only a small margin of improvement over the previous standard of care. More realistic estimates of the effect of the control regimen should be obtained from consensus estimates of the absolute control effect relative to no treatment. Preservation of a fraction of this larger effect would lead to more realistically sized prospective clinical trials. In fact, the ICH guideline E10 (Section 1.5.1.1, p.10) states: *"These studies should lead to the conclusion that the active control can consistently be distinguished from placebo in appropriately sized trials of design similar to the proposed trial and should identify an effect size that represents the smallest effect that the control can reliably be expected to have."* Alternatives for determining non-inferiority margins, such as that specified above, or use of an absolute margin (e.g., 0.8 for a hazard ratio) would allow for prospective clinical trials to address important scientific questions for new compounds that demonstrate important safety advantages over current standards of care. ICH guideline E10 concludes (Section 3, p.27): *"If a superiority trial is not feasible or is inappropriate for ethical or practical reasons, and if a defined treatment effect of the active control is regularly seen (e.g., as it is for antibiotics in most situations), a noninferiority or equivalence trial can be used and can be persuasive."* Specified alternatives for non-inferiority designs would promote consistency with other clinical trial endpoint and study design guidances globally.

Recommendation: We recommend that FDA convene a workshop or ODAC deliberation of non-inferiority issues and develop subsequent specific draft guidance to address this complicated and important topic. In the specific text of this guidance we recommend FDA indicate openness to multiple methods of non-inferiority trial designs (e.g., methodology for establishing non-inferiority margin), particularly in areas where new therapies offer safety advantages.

IV. Endpoints and Clinical Trial Design; Selected Issues

D. Isolating Drug Effect in Combination

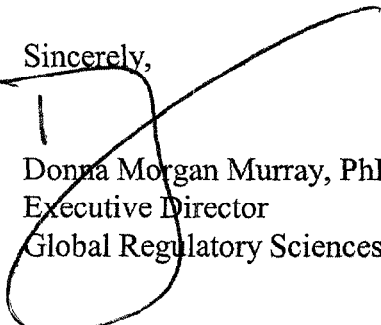
Lines 620-628: We suggest that this guidance acknowledge that the performance of multifactorial trials is not always possible in certain oncology settings to establish the contribution of component. As the standard of care in multiple settings is combination therapy, at times it is necessary (if an add on design is not feasible) to compare a new combination (generally with one or more drugs previously approved) to the current combination standard of care. There are precedents (docetaxel in NSCLC; oxaliplatin in CRC first line) that we recommend be specifically noted. We would also appreciate further guidance on approaches to support approval of combination regimens in these situations and particularly when safety superiority would be shown with non-inferior efficacy. Particular consideration of the design AB vs CD is an important consideration where CD is current best standard of care. In this case isolation of contribution of component of A and B may not be possible in traditional multifactorial trial manner. Additionally, the design AB vs CB could raise

question (where B is a well established therapy in combination use and CB is the standard of care). In this case the contribution of B can be inferred from historical use or data; however, the specific data demonstrating the efficacy component of A and B separately in the AB combination may not be possible or feasible given treatment standards in oncology clinical trials.

Recommendation: We recommend that FDA convene a workshop or ODAC deliberation of contribution or component for combination therapy regimens and develop a subsequent specific draft guidance to address this complicated and important topic. In the specific text of this guidance we recommend FDA indicate specific openness to multiple methods for demonstration of contribution of component, particularly in areas where new combination therapy regimens might offer superior efficacy over current standard of care.

BMS appreciates the opportunity to provide comment and respectfully requests that FDA give consideration to our recommendations. We would be pleased to provide additional pertinent information as may be requested.

Sincerely,



Donna Morgan Murray, PhD
Executive Director
Global Regulatory Sciences - Oncology & Neuroscience